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### III. REMARKS

#### Claim Status

Claims 1-13 stand rejected.

#### Claim Rejections - 35 USC § 112, 1<sup>st</sup> paragraph

Claims 1-13 stand rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement in that

1] claim 1 recites the phrase-"determining an environmental condition of which the effect on one or more microorganisms is unknown comprising measuring a natural biochemical composition...where said composition specifically changes...the induction route that leads to the change in the biochemical composition is unknown."

2] claims 2 and 3 recite nearly identical claim language to that of claim 1, particularly the limitations that the effect of the environmental condition on the microorganism is unknown and that the induction route that leads to the change in the biochemical composition is unknown.

3] claim 13 recites the phrase, "determining an environmental condition without identification of the effect of such environmental condition on one or more microorganisms comprising measuring a natural biochemical composition" in lines 1-4.

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The examiner states that it is unclear how one of skill in the art would be expected to know what natural biochemical composition to measure in said microorganism if the effect of the environmental condition on said microorganism is not identified.

With respect to this 112 rejection the examiner asks three pertinent questions.

First, the examiner asks how an environmental condition can be determined if the effect of the condition on the microorganism is unknown?

The answer is that the environmental condition - as is fully disclosed in the description - can be determined because it will cause effects [of some sort] in the microorganisms. Even without specific knowledge of the precise nature of those effects, the mere fact that changes have occurred will make it possible to compare the 'biochemical composition' of the microorganism with relation to a calibration set of biochemical compositions. Any change in the composition from the calibration set will be a reflection of the change in the environmental condition.

Next, the examiner asks how the environmental condition can be determined if the induction route that causes changes is unknown?

The response to this question is the same as that given to the first question. The biochemical composition is

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comprised of a plurality of different biomolecules of the microorganism (page 7, lines 18-20). Since a plurality of biomolecules is measured (for example, the total mRNA) the level of at least some of the individual biomolecules will be changed. This then can be regarded as the 'profile' for that environmental condition (without knowing what the function of the individual components is that make up this profile). This profile can then be analyzed with respect to (reference) profiles contained in a database. Thus, the change in the profile indicates a change in an environmental condition.

Next the examiner asks what characteristics or change in characteristics would one test for and how would the results be related to an environmental condition if the characteristic under a "standard" set of conditions [no environmental condition] were not also measured?

Applicants acknowledge the pertinence of this query and have amended claims 1 and 2 in response thereto. There is a comparison step introduced into the claims which now fulfills the requirement of a comparison standard.

Claim 3 already refers to a "calibration line" as the comparison.

Applicant respectfully refers the examiner to page 4, lines 13 et seq. of the specification where it is stated:

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"The present invention uses the principle that a microorganism reacts strongly to outside influences. The intrinsic changes in the microorganism after applying an external stimulus consist in changes in amounts and nature of biomolecules such as RNA, protein and metabolites. It has now been found that the sum total of such changes is characteristic of the nature of the external stimuli that the microorganism receives. Further, by measuring and comparing concentrations of these biomolecules in the microorganisms under various conditions, groups of biomolecules can be selected that specifically change as a result of a reaction of the microorganism under the influence of a specific stimulus or environmental condition."

The specification, at page 7, lines 15 et seq. states:

"A suitable collection of measuring results is formed by the transcriptional expression profile of a microorganism that can be obtained by measuring the different messenger RNA molecules present in the cell (transcriptome). The plurality of different biomolecules that is measured to deduce an environmental condition therefrom comprises, in that case, a plurality of different RNA molecules. An alternative collection of measuring results is formed by the protein expression profile of a microorganism, which is obtained by measuring

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the different protein molecules present in the cell (proteome). Another alternative is measuring the collection of metabolites (metabolome)."

The specification, at page 8, lines 13 et seq. states:

"Such biomolecules can comprise polynucleotides such as nucleic acids, (poly)peptides or proteins, polysaccharides, lipids, lipopolysaccharides and other cellular macromolecules. In this context, also metabolic intermediates such as sugars, organic acids, alcohols, fatty acids, amino acids, nucleotides and the like can be measured. In embodiments according to the present invention, nucleic acids can very suitably be measured, such as RNA, including messenger, transfer and ribosomal RNA or combinations thereof. With great preference, in the present invention, the biochemical composition of a microorganism is determined by determining the transcriptional status of the cell, i.e. measured in the form of messenger RNA."

The examiner also states that Applicant has given no guidance in the instant specification as to how one of ordinary skill in the art would determine what natural biochemical composition to measure, and whether the biochemical composition is something found in a microorganism, or in the environment.

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Applicant respectfully disagrees. As is stated in the specification, any number of biochemical compositions may be measured, whether the composition is present in the microorganism or released by the microorganism into the environment. It is the very point of the invention that multiple biochemical compositions ["plurality of different biomolecules", claim 1 lines 5-6] are measured to obtain the required profile. So a person skilled in the art, examining a ["plurality of different biomolecules" as required by the claims would *ipso facto* discover which are related to the specific environmental condition under consideration.

As stated on page 8 of the specification:

"Such biomolecules can comprise polynucleotides such as nucleic acids, (poly)peptides or proteins, polysaccharides, lipids, lipopolysaccharides and other cellular macromolecules. In this context, also metabolic intermediates such as sugars, organic acids, alcohols, fatty acids, amino acids, nucleotides and the like can be measured. In embodiments according to the present invention, nucleic acids can very suitably be measured, such as RNA, including messenger, transfer and ribosomal RNA or combinations thereof.

With great preference, in the present invention, the biochemical composition of a microorganism is determined by determining the transcriptional status of the cell, i.e. measured in the form of messenger RNA."

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With respect to the instant specification, Applicant states that "in principle, a large number of environmental conditions can be deduced therefrom, in principle without it being necessary that the induction routes that lead to the change are known."

The examiner states that applicant has provided no clear examples in the instant specification teaching one of skill in the art how to make and use the invention as claimed.

Applicant respectfully disagrees. As disclosed in the example spanning pages 13-20 a test was run utilizing *P. putida* and the results recorded demonstrating the usefulness of the claimed system. The specification also discloses the different biomolecules that may be utilized and the test procedures for utilizing those various biomolecules.

The only prerequisite for determining the "large number of environmental conditions" is that a change in conditions is reflected in a change to a biochemical marker or markers in a microorganism.

As discussed above, the induction route plays no part in the claimed methodology.

Contrary to the examiner's statement, as discussed above, Applicant has given guidance as to how one of skill in the art would determine an environmental condition, or determine a change in an environmental condition without knowledge of how the condition affects the microorganisms

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which are being exposed to it and experimentation within the scope of one skilled in the art to decide what biochemical compositions and biomolecules would need to be measured.

As amended, the claims reflect a procedure that compares the biochemical composition of the microorganism under the environmental conditions being examined against a calibration set or standard.

Therefore, applicant respectfully requests favorable reconsideration of this ground for rejection.

*Claim Rejections - 35 USC § 112, 2nd paragraph*

Claims 1-13 stand rejected under 35 U.S.C. 112, second paragraph, as being indefinite in that:

1] Claim 1 recites the phrase "measuring a natural biochemical composition by detecting qualitatively or quantitatively a plurality of different biomolecules..." in lines 3-4.

2] Claims 2 and 3 recite nearly identical claim language to that of claim 1, particularly the limitations involving measuring a biochemical composition by detecting biomolecules. It is unclear whether the biomolecules being detected are components of the natural biochemical composition, or whether they are something made by the microorganism in response to the presence of the biochemical composition and/or due to exposure to the environmental condition, or are something else entirely.

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Applicant respectfully disagrees with the statement that it is unclear what is being detected. As stated above, the specification clearly identifies the biomolecules:

"Such biomolecules can comprise polynucleotides such as nucleic acids, (poly)peptides or proteins, polysaccharides, lipids, lipopolysaccharides and other cellular macromolecules. In this context, also metabolic intermediates such as sugars, organic acids, alcohols, fatty acids, amino acids, nucleotides and the like can be measured. In embodiments according to the present invention, nucleic acids can very suitably be measured, such as RNA, including messenger, transfer and ribosomal RNA or combinations thereof.

With great preference, in the present invention, the biochemical composition of a microorganism is determined by determining the transcriptional status of the cell, i.e. measured in the form of messenger RNA." [spec. page 7, lines 12 et seq.]

Techniques for determining the biomolecules are specified at page 8, lines 29 et seq.:

"Suitable detection techniques that can be used in connection with above techniques are *inter alia* autoradiographic detection techniques, detection techniques based on fluorescence, luminescence or phosphorescence and chromogenic detection techniques. These techniques are well-known in the field of the detection of biomolecules.

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Preferably, in the present invention, the transcriptional status of a microorganism is measured by using techniques involving hybridization to arrays of nucleic acid probes or nucleic acid-mimicking probes."

3) Claims 1, 2, and 3 recite the phrase "the induction route that leads to the change in the biochemical composition is unknown." The examiner states it is unclear what exactly Applicant means by the term "induction route" and how one of skill in the art would be expected to know what biochemical composition to measure in a particular microorganism, what change in said composition to measure, and under what conditions said measurement should be made, in order to practice the claimed invention.

Applicant respectfully disagrees. First, there is no single biochemical composition to measure: a plurality is required by the claims.

Second, the change to measure is the quality or quantity of the plurality of biochemical compositions selected using standing measurement techniques known to those skilled in the art and which are different for each type of biomolecule.

Third, the conditions under which measurement should be made are the same conditions under which the calibration set was determined.

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The specification specifically discloses that there is not one specific biochemical composition that is required to be measured [spec. page 7, lines 15-20], that the change is dependent upon the biochemical composition being measured and that the measurement taken and the conditions are [spec. 8, 29 to 9,6] those that are ordinarily utilized by those skilled in the art who are taking the measurement.

How the environmental effect causes the resulting changes in the microorganism is irrelevant since applicant has described the biomolecules that should be measured. It is the change that is relevant, not the mechanism for the change.

Claim 13 recites the phrase, "determining an environmental condition without identification of the effect of such environmental condition on one or more microorganisms comprising measuring a natural biochemical composition" in lines 1-4 and stands rejected because the examiner states it is unclear how one of skill in the art would be expected to know what natural biochemical composition to measure in said microorganism if the effect of the environmental condition on said microorganism is not identified.

The response to this point is that there is a plurality of different biomolecules in a biochemical composition defined qualitatively or quantitatively by those biomolecules. The claim is directed to "measuring a natural biochemical composition by detecting qualitatively or quantitatively a plurality of different biomolecules ...

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where said composition specifically changes ...". Multiple biomolecules are selected and then measured to see if they have changed upon exposure to the environmental condition. The change, if any, defines the existence of the environmental condition.

Claims 1-3 and 13 recite the limitation "the effect" in line 1 and stand rejected because there is insufficient antecedent basis for this limitation in the claim.

The definite article "the" has been replaced with the indefinite article "an" thus obviating this ground for rejection.

All other claims depend directly or indirectly from rejected claims and, therefore, should be allowable under USC 112, second paragraph for the reasons set forth above.

***Claim Rejections - 35 USC § 103***

Claims 1-13 stand rejected under 35 U.S.C. 103(a) as being unpatentable over Duncan et al (Letters in Applied Microbiology 2000) in view of Larossa et al (US 6,607,885), and further in view of Bott et al (Water Science and Technology 2001).

Claims 1-11 stand rejected under 35 U.S.C. 103(a) as being unpatentable over Duncan et al. (Letters in Applied Microbiology 2000) in view of Larossa et al (US 6,607,885) and further in view of Bott et al. (Water Science and Technology 2001).

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In the first office action in the application, claims 1-11 were rejected under 35 U.S.C. 103(a) as being unpatentable over Duncan et al. (Letters in Applied Microbiology 2000) in view of Larossa et al (US 6,607,885).

Applicant traversed that rejection in their response to that office action and amended their claims in light of the rejection.

That rejection was withdrawn, and the current rejection which includes the Bott et al. reference was set forth in the last office action. In response to that office action, applicant discussed whether the addition of Bott et al. adds to the disclosure of the first two references which the examiner implicitly acknowledges do not render applicant's claims obvious.

In the new 35 USC 103(a) rejection, adding the Bott et al. reference to the combination of Duncan et al. and Larossa et al., the examiner states, at page 4 of the office action that Bott et al. teach

"that it is possible to identify a range of indicator proteins that are rapidly induced in response to stress and that these proteins provide valuable information about the health of the environmental system being studied (see for example, Abstract, and page 124)"

Applicant responded to the 103 rejection by discussing the inapplicability of Bott et al. to the instant disclosure and claims.

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The examiner states in the present current office action that, in their last response, applicants argued that Bott et al. merely contend that it may be possible to identify a range of indicator proteins that are induced in response to different mechanisms of stress in microorganisms.

The examiner considered this argument but rejected it stating "that Applicant may have taken out of context Bott et al.'s teachings, wherein the phrases quoted by Applicant were intended to showcase the concepts Bott et al. intended to test in the instant article. The examiner cites, for example, Bott et al, second full paragraph pg 124).

Applicants appreciate the examiner's candor in the suggestion that applicants may have misconstrued Bott et al. A further review of Bott et al. does, as the examiner suggests, showcase the concepts Bott et al. may have intended to test.

But in fact what Bott et al. did test was exactly what applicants stated in their last response: only the single protein GroHL. The intention to test a range of indicator proteins suggested by Bott et al. was never carried out. Regardless of the hypothetical testing Bott et al. may have intended to do the only disclosure was related to the single protein GroHL.

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For convenience sake applicants repeat the argument presented in their last response as it is believed it fully and fairly characterizes what Bott et al. does in fact teach.

In the new 35 USC 103(a) rejection, adding the Bott et al. reference to the combination of Duncan et al. and Larossa et al., the examiner states, at page 4 of the [previous] office action that Bott et al. teach

"that it is possible to identify a range of indicator proteins that are rapidly induced in response to stress and that these proteins provide valuable information about the health of the environmental system being studied (see for example, Abstract, and page 124)"

However, a reading of Bott et al. states differently. The Abstract of Bott et al. specified that the paper deals only with the heat shock protein, GroEL. The reference, on page 24, reads "we contend that it may be possible to identify a range of indicator proteins ... that are rapidly induced in response to different mechanisms of xenobiotic stress." [emphasis supplied]

This is not a disclosure of a scientific principle or a statement of scientific knowledge. Rather it is the musing of an experimenter who has not done any work to

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confirm or deny the possibility that the statement is true and who is so unsure of his ground that the most he is willing to say is that it "may be" possible.

The article then goes on to state that "it is important to establish preliminary relationships between stress protein induction patterns" in response to stressors.

Furthermore, in the second full paragraph of page 24, the authors state that they focused on monitoring "a single well characterized stress protein, GroEL."

Thus, at best, the article hypothetically suggests that since one protein can be used as a stress indicator, other proteins may also be used. It does not indicate that may be used simultaneously. It requires that induction patterns be established, at least preliminarily.

Thus, Bott et al. does not disclose the use of multiple protein indicators and furthermore requires that induction patterns be determined which teaches away from applicant's disclosure and claims.

In summary, nowhere does Bott et al. disclose anything other than the single protein GroHL.

Applicant notes that the instant claims recite detecting "a plurality of different biomolecules" rather than any one identified biomolecules. It is this vary plurality that allows applicants invention to function

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without requiring the preliminary knowledge required by the prior art and which the examiner has queried in the 112 rejection, regarding the necessity of knowing the induction route so as to choose the requisite biomolecules.

The power, usefulness, novelty and non-obviousness of applicants approach resides in the understanding that the utilization of a multiplicity of biomolecules frees the method from the strictures of the prior art.

Applicant respectfully submits that the amendments to the claims, as discussed above, also makes the invention unobvious over the references and believes these remarks and the claim amendments are sufficient to obviate the grounds for rejection presented in the outstanding office action and respectfully requests allowance of the pending claims. Please charge any insufficiency of fees, or credit any excess, to Deposit Account No. 14-1263.

Respectfully submitted,

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